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Review Article

Association Between Statin Use and Hepatocellular Carcinoma: A Meta-Analysis of Observational Studies

De-Sen Xiang, Jing Zhang*

Department of General Surgery, Qianjiang Central Hospital of Chongqing Municipality, Chongqing, China

Email address:
xderson@163.com (De-Sen Xiang), zj196810@126.com (Jing Zhang)

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Abstract: The relationship between statin use and the risk of hepatocellular carcinoma (HCC) remains controversial. Therefore, we conducted a meta-analysis to clarify this issue. Data on the relationship between statin use and the risk of HCC were collected through an electronic search of PubMed database. Summary odds ratios (ORs) with 95% confidential intervals were calculated using a random-effects model. Six studies were selected for the final meta-analysis, involving 3778 cases and 482452 patients. Our meta-analysis showed that statin use was significantly associated with a decreased risk of HCC (OR, 0.60, 95% confidence interval, 0.48–0.76). In conclusion, the meta-analysis suggests that statin use is associated with a reduced risk of HCC. However, our findings should be interpreted with caution due to limited studies.

Keywords: Statin, Hepatocellular Carcinoma, Meta-Analysis

1. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality, and the sixth most common cancer worldwide [1]. Half of these cases occur in China, where HBV and HCV are the major risk factors. By contrast, in western countries, 30% - 40% of HCC cases occur in patients with nonalcoholic fatty liver disease and metabolic diseases. For example, in the USA, nonalcoholic fatty liver is a main risk factor for HCC [2].

Statins are known as inhibitors of hydroxy-3-methylglutaryl coenzyme A, which are mainly used for the primary and secondary prevention of cardiovascular diseases [3]. Several experiments *in vivo* and *in vitro* have demonstrated that statins play a protective effect in the process of tumor formation [4-6]. These effects of statins are possibly mediated by effects of anti-proliferation, anti-angiogenesis, anti-oxidation, and anti-inflammation [7, 8].

Previous systematic reviews and meta-analyses have suggested that statin users were at a decreased risk of HCC [9-11]. However, a comprehensive review by Boudreau et al. did not suggest the aforementioned association [12]. The controversial results suggest a need for a more comprehensive meta-analysis. In addition, in recent years, several observational studies showed that statins might reduce the risk of HCC [13-16]. Given the huge burden of HCC and the widespread use of statins worldwide, establishing a definite association between statin use and the risk of HCC is of much importance for a better understanding of this association. With above considerations in mind, we performed this meta-analysis to investigate the association between statin use and the risk of HCC.

2. Methods

2.1. Search Strategy

We carried out an electronic search of PubMed database for observational studies published up to March 2015 on the association between statin use and the risk of HCC. The keywords used in the present study were "Hydroxymethylglutaryl-CoA reductase inhibitors", "HMG-CoA-reductase inhibitors", "statin", "simvastatin", "pravastatin", "lovastatin", "fluvastatin", "pravastatin", "atorvastatin", "liver cancer", "hepatocellular carcinoma", "hepatocarcinoma", "cancer" and "neoplasm".

2.2. Study Selection

The observational studies selected into this meta-analysis should conform the following criteria: (1) studying the

association between statin use and risk of HCC, (2) cohort or case-control study, (3) a defined diagnosis of HCC, (4) a clear definition of statin use exposure history. Inclusion was not restricted by publication. When there were multiple publications from the same research, the latest published research report was included.

2.3. Quality Assessment

In this paper, the Newcastle-Ottawa Scale (NOS) is used to evaluate the quality of included studies [17]. After judging three domains (selection, comparability and outcome), a maximum of 9 stars (four points for selection, two points for comparability, and three points for outcome) could be awarded to each study. We described the quality of included studies as high (6-9 points), moderate (4-5 points) and low (0-3 points). Any discrepancy was dealt with by discussion.

2.4. Data Abstraction

Relevant data were extracted as follows: the type of research design, research publication time, study region, the overall sample size, the number of HCC cases, the number of statins exposure group, risk estimates and 95% confidence interval (CI).

2.5. Statistical Analysis

Using the fixed-effects model or the random-effects model, we pooled the original data to calculate pooled OR and 95% CI by Review Manager 5.1. Heterogeneity between study-specific estimates was tested using the Q statistic and the I^2 statistic. If $P<0.10$ and $I^2>50\%$, the study will be considered to have statistically significant heterogeneity. Total effect size was synthesized by a random-effects model for data with significant inconsistency, otherwise by a fixed-effect model. Sensitivity analysis will be performed by omitting the heterogeneous study.

We used Begg's test and Egger's test to test publication bias. STATA software (version12.0, StataCorp, College Station, TX) was used to perform data synthesis and analysis. Statistical significance level was set at $P<0.05$ under two-sided test unless otherwise specified.

3. Result

3.1. Search Results

We identified 174 papers. On the basis of inclusion and exclusion criteria, 6 studies fulfilled our criteria, including 4 cohort studies and 2 case-control studies [18-23]. These studies reported a total of 3778 cases in 482452 patients (Fig. 1).

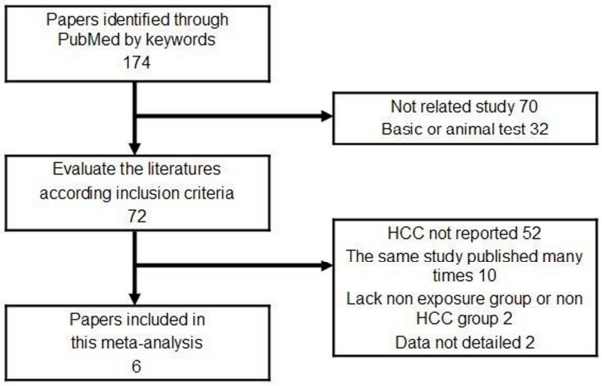

Fig. 1. *The flow chart of identifying relevant studies.*

Table 1. *The characteristics of six included studies.*

Study	Design type	Number of cases	Sample size	Region	Study period
Friis et al. (18), 2005	Cohort study	171	334754	Danmark	1989-2002
El-Serag et al. (19), 2009	Case-control study	1303	6515	America	2001-2002
Matsushita et al. (20), 2010	Cohort study	12	13724	Japan	2005-2010
Chiu et al. (21), 2011	Case-control study	1166	2332	Taiwan	2005-2008
Marelli et al. (22), 2011	Cohort study	105	91714	America	1991-2009
Tsan et al. (23), 2012	Cohort study	1021	33413	Taiwan	1997-2008

Table 2. *The results of quality assessment for included studies.*

Study	Choice of research object	Comparability between groups	Outcome measures	Total score
Friis et al. (18), 2005	4	1	3	8
El-Serag et al. (19), 2009	3	2	3	8
Matsushita et al. (20), 2010	3	1	3	7
Chiu et al. (21), 2011	3	2	2	7
Marelli et al. (22), 2011	4	2	3	9
Tsan et al. (23), 2012	3	2	3	8

3.2. Characteristics of Included Studies

The risk factors of HCC are varied widely across the studied population. In Asian studies, the main risk factors for HCC were HBV infection. By contrast, in Western studies, the main risk factors for HCC were alcoholic liver cirrhosis, non-alcoholic fatty liver, metabolic syndrome, diabetes. Friis et al. used data from the Danish Central Population Register and Danish Cancer Registry to identify 171 cases in 334,754 patients [18]. El-Serag et al. conducted a case-control study in 2001-2002 US veterans with diabetes. Matsushita et al performed an analysis in patients with hyperlipidemia in Japan

[19]. Chiu et al. conducted a case-control study on Taiwanese patients older than 50 years with a new diagnosis of HCC from 2005 to 2008 [20]. Marelli et al performed a cohort study of the incidence of cancer in older adults who had or had not used statins, using the General Electric Centricity electronic medical records database [21]. Tsan et al conducted a cohort study of patients with HBV with a new diagnosis of HCC from 1999 to 2008 [22]. The characteristics of these studies are shown in Table 1.

Using the NOS evaluation criteria, we took intensive studies included in this paper. Results of high quality were shown in all studies, and can be graded 7 points or higher (Table 2).

3.3. Meta-Analysis on Statin Use and the Risk of HCC

The summary OR was 0.60 (95% CI, 0.48–0.76) (P <0.01) (Fig. 2), showing that the use of statins can decrease the risk of liver cancer by 40%. There was no evidence of publication bias from the funnel plot (Fig. 3).

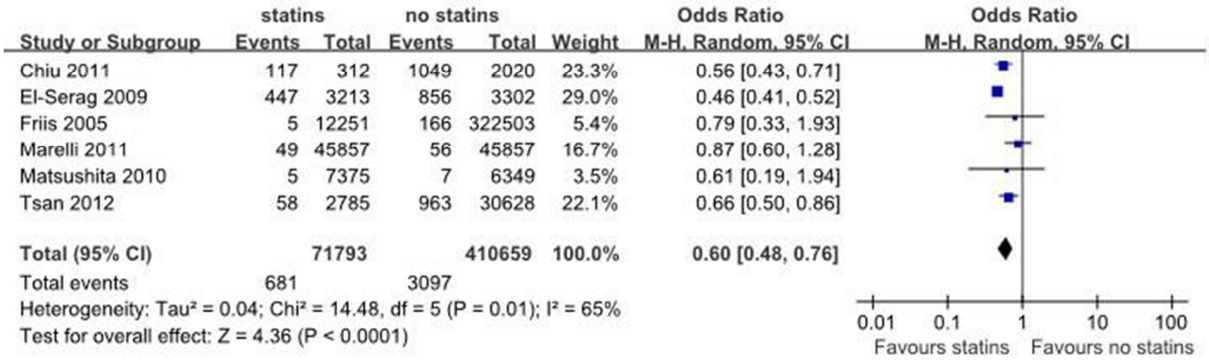

Fig. 2. *Forest plot of the HCC risk with statins exposure.*

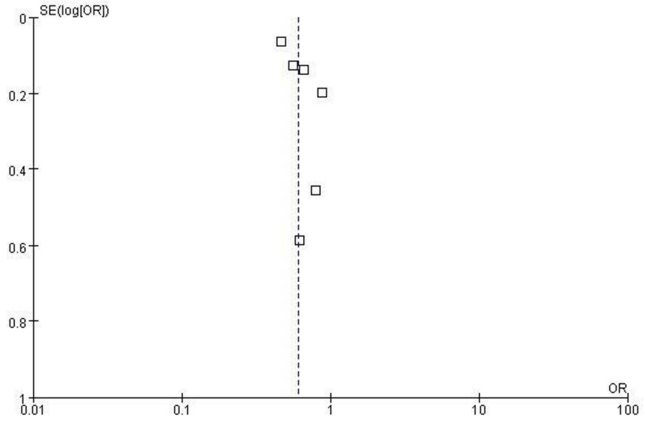

Fig. 3. *Funnel plot of the HCC risk with statins exposure.*

3.4. Subgroup Analysis

We performed a subgroup analysis based on the Asian population studies separately (Fig. 4). In this subgroup, P=0.67, I^2 = 0%, so the fix-effects model was used to combine data. The OR in Asian population was 0.60 (95% CI, 0.50–0.72), being closed to the overall OR. The Asian merging statistic test P< 0.01, so this subgroup analysis was statistically significant.

In this Asian subgroup analysis, use of statins was associated with a significant 40% risk reduction in the incidence of HCC. This drop degree was consistent with that of the overall study. Likewise, there was a significant 35% risk reduction in the incidence of HCC with statins use in the Western population. Our subgroup analysis suggested that statins played a protective role in Asia, where HBV infection was a high risk factor of HCC. In addition, this group could partly explain the significant heterogeneity seen in the overall analysis.

Sufficient data were not available to perform stratified analyses based on age, sex, statins type, statins dose, or statins duration.

3.5. Influence Analysis

In order to further explore the sources of heterogeneity between studies, additional influence analysis was performed. We found that heterogeneity was largely because of study by El-Serag et al [19]. When omitting it, the I^2 dropped to 2% (P=0.40), whereas the summary OR was only marginally modified (OR, 0.65, 95% CI, 0.55–0.76). This merging statistic test P< 0.01, so this analysis was statistically significant. Detail is shown in Fig. 5.

When omitting study by El-Serag et al [19], the I^2 dropped significantly, whereas the summary OR was only marginally modified. Conversely, neither the heterogeneity nor the summary OR was influenced by omitting the other study. So study by El-Serag et al [19] was the major source of heterogeneity. We found that in the study by El-Serag et al [19], population was US veterans with diabetes in 2001-2002. The insulin resistance of diabetes patients can result in lipid metabolic disorders, and nonalcoholic fatty liver disease. Diabetes exists cellular immune regulating function disorder, becomes a liver cancer risk factors [18]. In western populations, the high risk factors of HCC are nonalcoholic fatty liver disease, diabetes and metabolic syndrome. In other words, in the study by El-Serag et al [19], population had a higher risk than any other group of study, which affected the whole heterogeneity. From this analysis, not only could well explain the source of heterogeneity, but also could prove the reliability of the analysis.

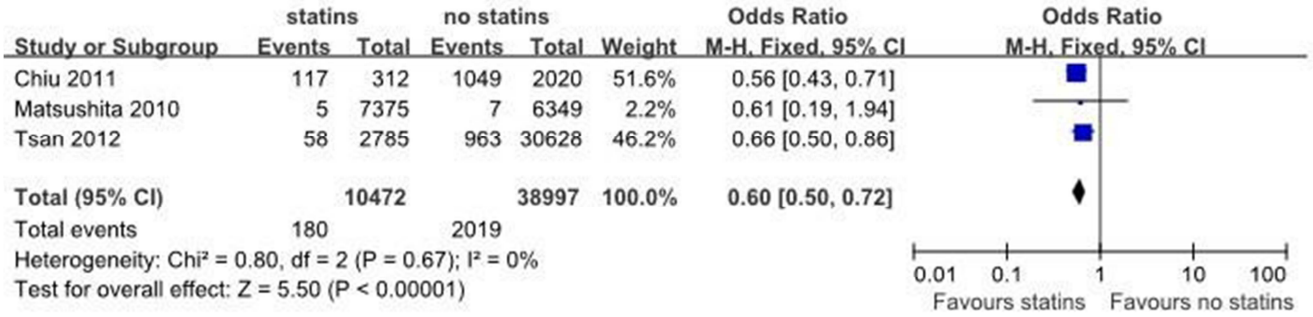

Fig. 4. *Forest plot of the HCC risk with statins exposure in Asian population.*

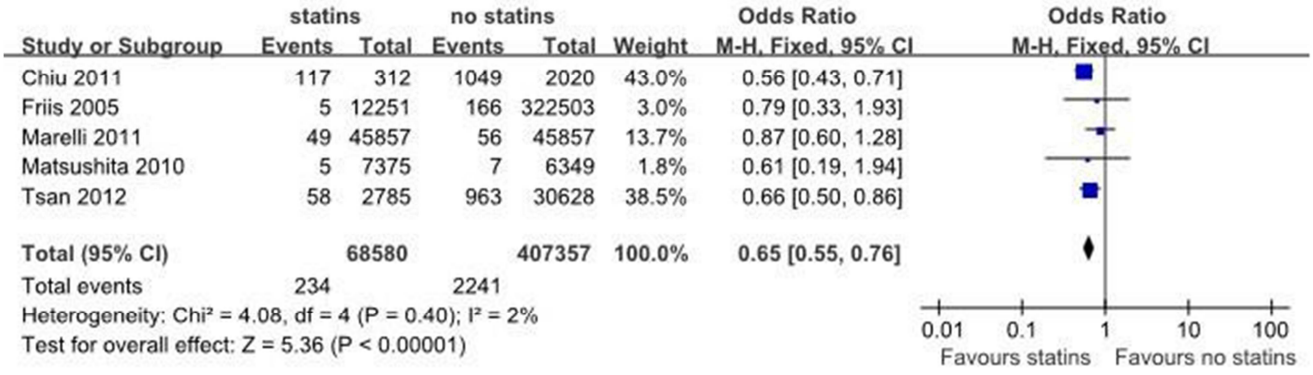

Fig. 5. *Forest plot after omitting the study by El-Serag et al.*

4. Discussion

4.1. Main Findings

This paper analyzed six studies reporting 3778 cases of HCC in 482452 patients. After combining the original data by the random-effects model, the summary random-effect OR was 0.60 (95% CI, 0.48–0.76), and the P-value was less than 0.01. The OR and the upper limit of 95% CI was less than 1, so statins had a protective effect on HCC risk. As this result, we found that statin use is associated with a significant 40% reduction in the risk of HCC. This effect was more pronounced and consistent in the Asian population.

All studies included in this meta-analysis could be graded 7 NOS points or higher, could be considered high quality literature. The funnel chart showed no significant publication bias into literature. While there was heterogeneity between studies, but the source of heterogeneity was clear. Ignoring heterogeneity research, the consistency between the rests of the study was very well. The subgroup analysis was consistent with the overall study. The influence analysis was stable. So this meta-analysis was basically believable.

4.2. Anti-tumor Effect of Statins

At present the mechanism of statins reducing HCC risk is not clear. Some relevant research had put forward some possible potential mechanisms. Friis and Tsan study included the non-statin lipid-lowering medicine group, and pointed out that the non-statin lipid-lowering drug had no effect on HCC risk. So the protective effect of statins should have nothing to do with the lowering blood lipid effect [7, 8].

In vitro and animal studies have shown that statins exert anti-neoplastic effects through both HMG-CoA reductase–dependent and HMG-CoA reductase–independent pathways. By competitive inhibition of HMG-CoA reductase, and blocking the conversion of HMG-CoA into mevalonate, statins can inhibit several downstream products of the mevalonate pathway, including the generation of isoprenoids. This prevents posttranslational prenylation of small signaling G proteins of the Ras/Rho family, which are important mediators of cell growth and survival. They also exert proapoptotic effects through regulation of the RAF/mitogen-activated protein kinase 1/extracellular signal–regulated kinase (MEK-ERK) pathway [24]. Statins inhibit the activation of the proteasome pathway, limiting the breakdown of cyclin-dependent kinase inhibitors p21 and p27, thus allowing these molecules to exert their growth-inhibitory effects [25]. In addition, they exert anti-inflammatory and immunomodulatory effects, modifying the cell adhesion cascade [2].

Myc activation is a critical step in hepatocarcinogenesis [26]. In a transgenic model of Myc-induced HCC as well as in human HCC-derived cell lines, statins could block Myc phosphorylation and activation, suppressing tumor initiation and growth. Shimizu et al showed that pitavastatin can inhibit the early phase of obesity-related liver tumorigenesis [27].

Demierre et al [2] and Argo et al [28] studies had shown that statins have a potential chemical anti-cancer effect.

It is found that high expression of microRNA-519a is associated with adverse clinicopathological characteristics, such as large tumor size and advanced tumor-node-metastasis tumor stage. Tu et al. found that phosphatase and tensin homolog (PTEN) was a direct target and a downstream mediator of the biological function of microRNA-519a in HCC [29]. Therefore, PTEN is also involved in cancer development. Interestingly, simvastatin has been found to increase PTEN expression in an animal model [30], thus it potentially serves as a novel prognostic bio-marker and therapeutic target for HCC. Nevertheless, it must also be studied in liver pathology before formal clinical application.

4.3. Differences Between Asian and Western Populations

Statins chemical anti-cancer effects of HCC in Asia and the western populations were very obvious; this effect was more obvious in Asia population. In most of Asia, HBV infection is the high risk factor of the HCC, whereas it accounts for only 23% of HCC cases in the western developed countries. In the United States and several other western countries, alcohol-related cirrhosis, non-alcoholic fatty liver disease, obesity and the metabolic syndrome are thought to be the main risk factors of liver cancer.

In Asian population, HBV infection is the high risk factor of the HCC. HBV genome integration has been associated with host DNA micro deletions that can target cancer-relevant genes, potentially providing these cells with a growth advantage [31]. In addition, HBV protein X transcriptional activation activity can alter the expression of several growth control genes, such as Ras, Raf, ERK, MAPK, and so on [32]. By inhibiting the mevalonate pathway, statins can prevent potential detrimental effects of these growth signaling proteins. Likewise, statins also can inhibit HCV to stimulate the nuclear factor κB pathway, which lead to immune activation and inflammation [33]. By down-regulation of growth arrest gene, HCV also can promote cell growth. This effect can be inhibited by statins [34].

Unlike the Asian population, the mechanisms by which statins alter the risk of HCC in the Western population may be related to modification of metabolic syndrome, insulin-mediated cell proliferation, and obesity-associated inflammation. Diabetes is an important risk factor of HCC in West [18]. Insulin resistance in diabetic patients can cause lipid metabolic disorders. Glucose and fatty acids can't be used very well, and the lipoprotein synthesis process is inhibited. Eventually the fatty acids are stored in the liver. The liver is developing to be nonalcoholic fatty liver disease step by step. Due to the higher level of insulin in diabetes patients, mitochondrial β oxidation process of the fatty acid is inhibited. The liver is stimulated by chronic inflammation repeatedly, easy to malignant change. Insulin resistance can cause lipid peroxidation, producing some by-products, such as 4-hydroxynonenal which may participate in mutation of the p53 tumor suppressor gene. At the same time, high blood sugar can produce a large number of free radicals, which can induce oxidative stress and DNA mutation. Long-term high blood sugar can be used as nutrients for the growth of tumor cells. Patients with diabetes have regulatory dysfunction of cellular immunity, leading to anti-tumor immune function decline. If diabetic patients are suffering from hepatitis, the risk of cancer will increase greatly. Sulfonylureas anti diabetes drugs also may increase the risk of HCC. These explained the causes of large heterogeneity between El-Serag study and other studies. But at present the mechanisms by which statins alter the risk of HCC in the Western population are unclear.

4.4. The Effect of Statins Dose, Duration and Type

Due to the different design of each group, a lot of research didn't have a clear definition about the statin dose and duration. So the meta-analysis of dose and duration effects of statins couldn't be carried out. Tsan et al reported that a high doseduration statin product was associated with greater protective effects on HCC in their cohort. El-Serag et al study had shown that, statin use for more than 6 months was associated with a significant decrease in risk of HCC, although no significant differences were found between the patients in the lowest dose-duration as compared with the highest dose-duration. In addition, Chiu et al found no clear dose-effect relationship, and the daily low-dose had no obvious difference with the daily high-dose in incidence of HCC. Weis et al [35] research showed that statins have a dose dependent effect in the angiogenesis, pro-angiogenesis effect in small dose, and anti-angiogenesis effect in large dose.

Due to greater lipid solubility and membrane permeability, the lipophilic statins may have a greater protective effect than the lipophobic statins. In fact, Tsan et al reported no significant differences in the risk reduction of HCC with hydrophilic or lipophilic statins. These unclear issues need to be further researched to explore.

4.5. Hepatotoxicity of Statins

The hepatotoxicity of statins is always a concern for clinicians and patients in clinical practice. For patients with chronic liver diseases, many physicians continue to avoid statins in subjects with chronic liver disease due to the possibility of the elevation of liver enzymes and liver injury. Indeed, a case series study found that the risk of jaundice was obviously higher than has been previously estimated in patients on statins [36]. However, many studies have identified the safety of statins in subjects with chronic liver disease [37, 38]. Generally, the hepatotoxicity of statins appears to happen in less than 3% of all subjects on statins. Moreover, if the hepatotoxicity of statins occurs, it possibly spontaneously resolves. Thus, if the protective effect of statins on HCC is confirmed, clinicians should not hesitate to prescribe statins for patients with chronic liver diseases.

4.6. Limitations

The observational studies lack experimental distribution randomness. The confounding factors cannot be controlled

very well at the same time. So the exposure-effect relationship can't to be evaluated very well, the true effect may be assessed too high. All studies included were observational studies. The diagnosis of HCC was based on the medical diagnostic criteria, there might be undiagnosed clinically silent HCC to be divided into non HCC groups. In addition, observational studies may be subject to recall bias. The literature searched was limited to Chinese and English, there might be some selection bias.

Cholesterol metabolism is the most important physiological function of liver, so statins block effect for this path may be associated with liver toxicity. Statins common untoward effect is the rise of liver enzyme levels. At present clinical statins are rarely used in patients with chronic liver disease [39]. On the one hand, statins can prevent chronic liver disease developing to HCC. On the other hand, statins can increase the level of liver enzymes, and influence or damage the liver function. So whether patients with chronic liver disease can use statins deserves to be researched further.

5. Conclusion

This meta-analysis suggests that use of statins is associated with a reduced risk of HCC, and statins is playing a protective role in the risk of HCC.

But due to the restrictions of observational studies, the effect of statins may be thought highly. In order to make the argument more convincing, randomized controlled trial is needed. At the same time whether patients with chronic liver disease can use statins is worth to verify by further experiments.

List of Abbreviations

CI, confidence interval; HCC, hepatocellular carcinoma; NOS, Newcastle-Ottawa Scale; OR, odds ratio.

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